CERTIFICATE OF MAILING (37 CFR 1.10)

"Express Mail" No.: TB689488536 US **Date of Deposit:** June 24, 1996

I hereby certify that this transmittal together with the patent application referred to below is being deposited with the United States Postal Service "Express Mail Post Office to Addressee" service under 37 CFR 1.10 on the date indicated above and is addressed to the Commissioner of Patents and Trademarks, Washington, DC 20231.

Julie Lyons, Legal Technician — Julie Lyons

Name of Person Mailing Paper — **Signature**

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant	:	Pharmacia & Upjohn Company (formerly The Upjohn Company)
Patent No.	:	4,902,683
Issue Date	:	20 February 1990
Patent Title	:	CRYSTALLINE CEPHALOSPORIN HYDROHALIDE SALTS

Commissioner of Patents and Trademarks
Washington, DC 20231

APPLICATION FOR EXTENSION OF PATENT TERM UNDER 35 USC 156

Your Applicant, Pharmacia & Upjohn Company (formerly The Upjohn Company) (a copy of the Certificate of Amendment showing the name change is attached hereto as "Appendix A-2") represents that it is the Assignee of the entire interest in and to Letters Patent of the United States No. 4,902,683, issued to your Applicant, with inventors, Mahendra I. Amin and Jay A. Campbell, on the 20th day of February 1990, titled "CRYSTALLINE CEPHALOSPORIN HYDROHALIDE SALTS." Your Applicant, acting through the undersigned attorney, hereby submits this application for extension of patent term under 35 USC 156 by submitting the following information required by 37 CFR 1.740. An original of the Power of Attorney is attached hereto as "Appendix A-1."

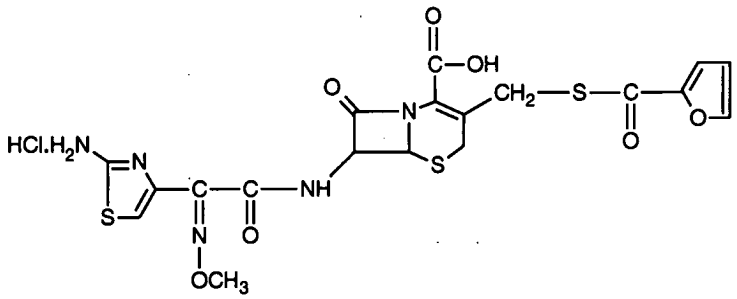
1. **Identification of Approved Product**

230 DD 21-0718 07/02/96 4902683
1,080.00CH

The approved product is EXCENEL® Sterile Suspension. Ceftiofur hydrochloride is the active ingredient in EXCENEL® Sterile Suspension which is an injectable animal

drug for treating swine respiratory disease. Ceftiofur hydrochloride is a chemical compound also known as:

- Upjohn Laboratory Code: U-64279A;
- Chemical Abstracts Services (CAS) Registry Number: CAS-103980-44-5;
- Chemical Name: 5-Thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid, 7-[[(2-amino-4-thiazolyl)(methoxyimino)acetyl]amino]-3-[[(2-furanylcarbonyl)thio]methyl]-8-oxo, monohydrochloride, [6R-[6α,7β(Z)]]-;
- United States Adopted Name (USAN) or Generic Name: Ceftiofur Hydrochloride;
- Molecular Formula: $C_{19}H_{17}N_5O_7S_3$ (HCl);
- Molecular Weight: 560.01;
- Chemical Structure:



2. **Federal Statute and Applicable Provision Under Which Regulatory Approval Occurred**.

Section 512(c) of the Federal Food, Drug and Cosmetic Act.

3. **Date Permission Received For Commercial Marketing and Use**.

The Upjohn Company (now Pharmacia & Upjohn Co., as noted above) first received permission for commercial marketing and use of EXCENEL® Sterile Suspension under Section 512(c) of the Federal Food, Drug and Cosmetic Act (21 USC 360b(c)) on 26 April 1996.

4. **Identification of Active Ingredient in Drug Product and Statement That It Has Not Been Previously Approved For Commercial Marketing or Use Under the Federal Food, Drug and Cosmetic Act, the Public Health Service Act or the Virus-Serum-Toxin Act.**

The active ingredient of EXCENEL® Sterile Suspension is ceftiofur hydrochloride. Ceftiofur hydrochloride has not been previously approved for commercial marketing or use under the Federal Food, Drug and Cosmetic Act, the Public Health Service Act, or of the Virus-Serum-Toxin Act.

The active ingredient of NAXCEL® Sterile Powder is ceftiofur sodium. Ceftiofur sodium was previously approved for commercial marketing or use under the Federal Food, Drug and Cosmetic Act.

Ceftiofur hydrochloride is not a salt or ester of ceftiofur sodium.

5. **Statement That the Application Is Being Submitted Within the 60-Day Period Permitted For Submission and the Last Day On Which the Application Can Be Submitted.**

This application for patent term extension is being submitted pursuant to 37 CFR 1.720(f) within sixty (60) days of the date 26 April 1996. The last day on which this application could be submitted is 25 June 1996.

6. **Identification of Patent For Which Extension Is Being Sought.**

Patent No.	:	4,902,683
Names of Inventors	:	Mahendra I. Amin and Jay A. Campbell
Issue Date	:	20 February 1990
Expiration Date	:	20 February 2007

7. **Copy of Patent**

A copy of the patent identified in paragraph 6 hereof is attached as "Appendix B."

8. **Copies of Disclaimers, Certificates of Correction, Receipt of Maintenance Fee Payments and Re-examination Certificates.**

No disclaimers have been made, nor have any certificates of correction or re-examination certificates issued with respect to U.S. Patent 4,902,683. The Maintenance fees under 37 CFR 1.20(e) for this patent are not now due; and it is the intent of the Applicant to pay the Maintenance fees as they come due.

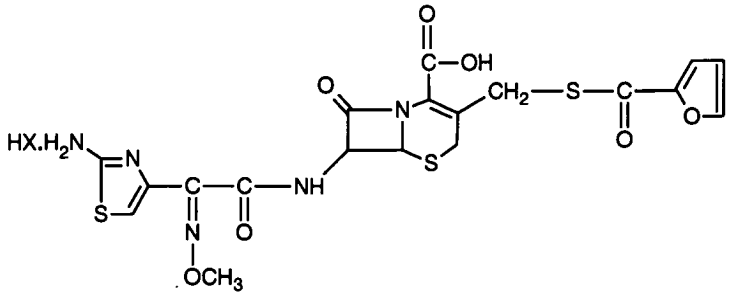
9. **Statement That Patent Claims the Approved Product or Method of Using the Approved Product and Demonstration That Applicable Patent Claims Read on the Approved Product and Methods of Use.**

U.S. Patent 4,902,683 claims ceftiofur hydrochloride, which is the active ingredient of the approved product, EXCENEL® Sterile Suspension. This patent describes the preparation of ceftiofur hydrochloride, for example, at Col. 2, lines 3-48; Col. 3, lines 25-64; Col. 4, line 56, through Col. 5, line 59; and Examples 1-4 at Col. 7, line 41, through Col. 8, line 68; and states at Col. 5, line 60, through Col. 6, line 3, that the compound of the invention is useful for treating bacterial infections in valuable mammalian animals.

Therefore, U.S. Patent 4,902,683 discloses the preparation and use of ceftiofur hydrochloride, and in claims 1-13, claims the compound *per se*, a process for preparing it, a pharmaceutical composition containing it and a method of using. Specifically, the claims of this patent read on ceftiofur hydrochloride, the active ingredient of the approved product, as follows **A-D**:

A. The compound is claimed *per se* in claims 1, 2, 3, 4 and 5 as follows:

1. A cephalosporin hydrohalide compound of the formula



wherein X is chloride or bromide.

2. A compound according to claim 1 where X is chloride.

3. A crystalline compound according to claim 1.

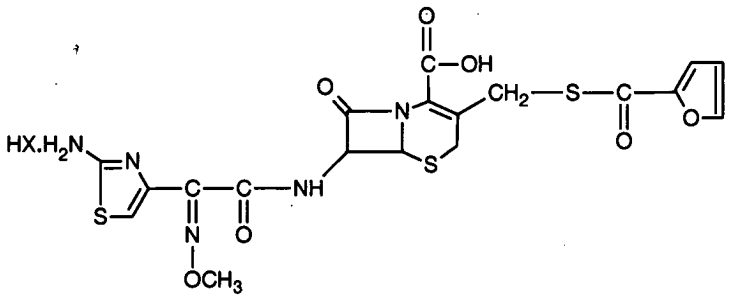
4. A crystalline compound according to claim 2.

5. A compound according to claim 4 which has the following x-ray powder diffraction pattern when crystallized from an acetone/water mixture.

Interplanar d-spacings	intensity (relative %)
18.4	44.2
12.4	73.1
8.26	50.0
7.82	100.0
7.69	17.9
6.19	48.1
5.86	32.1
5.21	23.1
5.12	40.4
4.74	30.1
4.37	21.8
4.23	13.5
3.98	26.9
3.91	35.9
3.81	17.9
3.30	14.1
3.01	12.8
2.88	14.1

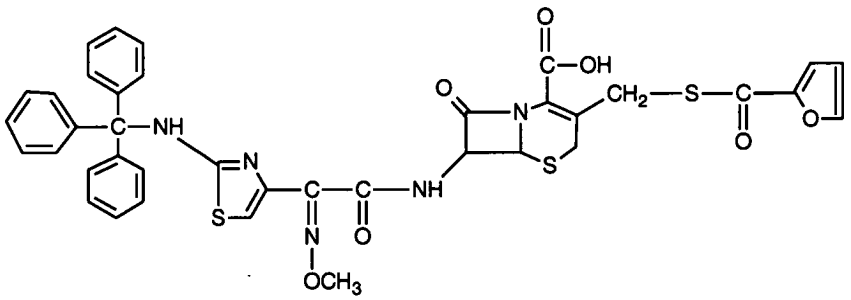
B. A process for preparing ceftiofur hydrochloride is claimed in claims 6-9 as follows:

6. A process for preparing a crystalline cephalosporin hydrohalide salt of the formula



where X is chloride or bromide, which comprises the steps of

(a) treating the N-tritylamino cephalosporin compound of the formula



with a solution of a polar organic solvent and water and hydrogen halide, where halide is chloride or bromide, in an amount which is at least stoichiometrically equivalent to the amount of the N-trityl compound (3) in the mixture,

(b) heating the mixture from step (a) to a temperature of at least 45°C and for a time sufficient to effect detritylation,

(c) decreasing the concentration of the polar organic solvent in the aqueous phase of mixture from step (b) to effect formation of crystalline cephalosporin hydrohalide salt (1),

(d) separating the crystalline cephalosporin hydrohalide salt from the slurry mixture from step (c),

(e) washing the separated crystalline cephalosporin hydrohalide salt from step (d) with water and polar organic solvent, and drying the washed crystalline cephalosporin hydrohalide salt from step (e).

7. A process according to claim 6 wherein the crystalline cephalosporin hydrohalide salt of Formula 1 being prepared is the hydrochloride salt.

8. A process according to claim 7 wherein in step (c) of the process, toluene is used as the non-polar, water immiscible organic liquid to separate by-product trityl alcohol and to decrease the quantity of the polar organic liquid in the aqueous phase of the mixture.

9. A process according to claim 7 wherein step (c) of the process heptane is used as the non-polar, water immiscible organic liquid to separate trityl alcohol by-product and the mixture is distilled to remove polar organic liquid therefrom to enhance formation of the crystalline cephalosporin hydrochloride.

C. A pharmaceutical composition comprising ceftiofur hydrochloride is claimed in claims 10-11 as follows:

10. A pharmaceutical composition useful in pharmaceutically effective dosage unit form for alleviating the effects of undesired bacterial infections in warm-blooded mammals which comprises a compound according to claim 1 in combination with a pharmaceutically acceptable carrier.

11. A composition according to claim 10 wherein the compound is ceftiofur hydrochloride.

D. A method of using ceftiofur hydrochloride is claimed in claims 12-13 as follows:

12. A method for alleviating the effects of undesired bacterial infections in a warm-blooded animal which comprises administering to an animal suffering such a bacterial infection an effective amount of a compound of claim 1 in a pharmaceutically acceptable dosage unit form.

13. A method according to claim 12 wherein the active compound is ceftiofur hydrochloride.

10. **Relevant Dates During Regulatory Review**

Relevant dates and information pursuant to 35 USC 156(g) to enable the Examiner of Health and Human Services to determine the applicable regulatory review period are set forth below.

Because this new animal drug product was the subject of much diligent research and development activity before government agencies, its regulatory history is somewhat complex. (A complete chronology of these activities is attached hereto as "Appendix C.") Therefore, Applicant has set forth below two alternative methods (Scenarios I and II) for determining the applicable regulatory review periods for the present application:

Scenario I:

The Investigational New Animal Drug (INAD) application 4601 for ceftiofur hydrochloride for the treatment of bovine respiratory disease was filed on 29 August 1985. The FDA acknowledged this filing for this drug on 12 December 1985 (effective date). Upjohn worked with due diligence on this drug under this INAD from this date until the present and continues to work under this INAD, as evidenced by the chronology for INAD 4601 attached hereto. Some of the studies conducted under this INAD were considered essential for the approval of the present NADA 140-890.

The New Animal Drug Application (NADA) 140-890 for ceftiofur hydrochloride for the treatment of bovine respiratory disease was filed on 30 March 1988. Upjohn worked with due diligence on this drug under this NADA, as evidenced by the chronology for NADA 140-890 attached hereto. Many submissions were made under this NADA from 22 March 1990 (a date after U.S. Patent 4,902,683 issued) until 5 October 1993.

The Investigational New Animal Drug (INAD) application 9138 for ceftiofur hydrochloride for the treatment of swine respiratory disease was filed on 5 November 1993. The FDA acknowledged this filing for this drug on 10 November 1993 (hereinafter "effective date"). Upjohn worked with due diligence on this drug under this INAD from this date until the drug was approved on 26 April 1996.

Under FDA Policy Guide 1240.3040 and CVM's Document and Submission Information Update, dated April 1995, pivotal portions of NADA 140-890 were submitted for phased review under INAD 9138 as follows:

1) INAD Filing: 5 November 1993
2) Human Food Safety: 2 March 1995

3)	Environmental Assessment:	28 March 1995
4)	Target Animal Safety:	2 March 1995
5)	Efficacy:	2 March 1995
6)	Metabolism Chemistry	2 March 1995
7)	Manufacturing Chemistry:	16 August 1995
8)	Administrative NADA Filing:	3 April 1996

The Administrative NADA 140-890 for ceftiofur hydrochloride for the treatment of swine respiratory disease was submitted on 3 April 1996. NADA 140-890 for ceftiofur hydrochloride was approved for marketing in the United States on 26 April 1996.

Scenario II:

The Investigational New Animal Drug (INAD) application 9138 for ceftiofur hydrochloride for the treatment of swine respiratory disease was filed on 5 November 1993. The FDA acknowledged this filing for this drug on 10 November 1993 (hereinafter "effective date"). Upjohn worked with due diligence on this drug under this INAD from this date until the drug was approved on 26 April 1996.

Under FDA Policy Guide 1240.3040 and CVM's Document and Submission Information Update, dated April 1995, pivotal portions of NADA 140-890 were submitted for phased review under INAD 9138 as follows:

1)	INAD Filing:	5 November 1993
2)	Human Food Safety:	2 March 1995
3)	Environmental Assessment:	28 March 1995
4)	Target Animal Safety:	2 March 1995
5)	Efficacy:	2 March 1995
6)	Metabolism Chemistry	2 March 1995
7)	Manufacturing Chemistry:	16 August 1995
8)	Administrative NADA Filing:	3 April 1996

The Administrative New Animal Drug Application (NADA) 140-890 for ceftiofur hydrochloride for the treatment of swine respiratory disease was filed on 3 April 1996. NADA 140-890 for ceftiofur hydrochloride was approved for marketing in the United States on 26 April 1996.

11. **Brief Description of Activities Undertaken By Applicant During the Applicable Regulatory Period With Respect to the Approved Product and the Significant Dates Applicable to Such Activities.**

A brief description of the development activities undertaken by The Upjohn Company during the applicable regulatory review period with respect to ceftiofur hydrochloride and significant dates applicable to such activities are attached hereto as "Appendix C" and is a chronology of communications between The Upjohn Company and the FDA between 29 August 1985 and 26 April 1996 regarding INADs 4601 and 9138 and NADA 140-890.

12. **Applicant's Opinion As to Why the Patent is Eligible for Patent Extension and How the Length of Extension Was Determined.**

Applicant believes that U.S. Patent No. 4,902,683 is eligible for an extension under 35 USC 156 because it satisfies all of the requirements for such extension including, inter alia, the following:

(a) 35 USC 156(a):

U.S. Patent 4,902,683 claims a new animal drug product.

(b) 35 USC 156(a)(1):

The term of U.S. Patent 4,902,683 has not expired prior to submission of this application for extension.

(c) 35 USC 156(a)(2):

The term of U.S. Patent 4,902,683 has never been extended;

(d) 35 USC 156(a)(3):

This application for extension is submitted by the owner of record of U.S. Patent 4,902,683 in accordance with the requirements of 35 USC 156(d) and 37 CFR 1.710 et. seq.

(e) 35 USC 156(a)(4):

The approved product EXCENEL® Sterile Suspension was subject to regulatory review prior to its commercial marketing or use.

(f) 35 USC 156(a)(5)(A):

Permission for the commercial marketing or use of the product, EXCENEL® Sterile Suspension, after the regulatory review period is the first permitted commercial marketing or use of the product (ceftiofur hydrochloride) under the provisions of the FDC Act (21 USC 355) under which such regulatory period matured;

(g) 35 USC 156(c)(4):

No other patent has been extended for the same regulatory review period for the product EXCENEL® Sterile Suspension (ceftiofur hydrochloride).

Determination of Length of Extension

The length of extension of the patent term of U.S. Patent 4,902,683 claimed by Applicant is from a minimum period of 1 year, 3 months and 4 days to a maximum period

of 3 years, 2 months and 6 days under 35 U.S.C. 156(g), calculated in Scenarios I and II as follows: (In these calculations, it is assumed that 30 days equal 1 month; also half-days are ignored.)

Scenario I:

The length of extension of the patent term of U.S. Patent 4,902,683 claimed by Applicant is 3 years, 2 months and 6 days pursuant to 35 U.S.C. 156(g) as follows:

a) One half of the INAD regulatory review period for the approved product beginning 10 November 1993 (the INAD "effective date") and ending on 2 April 1996 (one day prior to the date on which the NADA for the approved product was initially submitted), such sum being equal to 1 year, 2 months and 11 days.

b) The term of the NADA regulatory review period commencing on 22 March 1990 (the date of the first submission to the NADA after U.S. Patent 4,902,683 was issued) to 5 October 1993 and the period commencing on 3 April 1996 (the date the NADA for the approved product was originally submitted) and ending on 26 April 1996 (the date on which the NADA was approved), such sum being equal to 3 years, 7 months and 6 days.

c) The sum of paragraphs (a) and (b) in this subsection equals 4 years, 9 months and 17 days.

d) This sum is limited to 3 years, 2 months and 6 days because under 35 U.S.C. 156(c)(3) the period of extension cannot exceed a patent life of 14 years from the date of NADA approval. The original term of U.S. Patent 4,902,683, after NADA 140-890 was approved, was 10 years, 9 months and 25 days (26 April 1996 to 20 February 2007); therefore, a period of extension of 3 years, 2 months and 6 days will give U.S. Patent 4,902,683 a life equal to 14 years.

e) This sum is not limited under 35 USC 156(g)(6)(A) which states that if the patent involved is issued after the date of enactment of this section, the period of extension may not exceed 5 years. The period of this extension is 3 years 2 months and 6 days, which is less than 5 years.

f) Applicant herewith, claims an expiration date of 26 April 2010 for U.S. Patent 4,902,683 pursuant to 35 U.S.C. 156.

Scenario II:

Alternatively, the length of extension of the patent term of U.S. Patent 4,902,683 claimed by Applicant is 1 year, 3 months and 4 days pursuant to 35 U.S.C. 156(g) as follows:

a) One half of the INAD regulatory review period for the approved product beginning 10 November 1993 (the INAD "effective date") and ending on 2 April 1996 (one day prior to the date on which the NADA for the approved product was initially submitted), such sum being equal to 1 year, 2 months and 11 days.

b) The term of the NADA regulatory review period commencing 3 April 1996 (the date the NADA for the approved product was originally submitted) and ending on 26 April 1996 (the date on which the NADA was approved), such sum being equal to 23 days.

c) The sum of paragraphs (a) and (b) in this subsection equals 1 year, 3 months and 4 days.

d) This sum is not limited under 35 U.S.C. 156(c)(3) which states that the period of extension cannot exceed a patent life of 14 years from the date of NADA approval. The original term of U.S. Patent 4,902,683, which remained after NADA 140-890 was approved, was 10 years, 9 months and 25 days (26 April 1996 to 20 February 2007); therefore, a period of extension of 1 year, 3 months and 4 days will give U.S. Patent 4,902,683 a life equal to 12 years and 29 days, which is less than 14 years.

e) This sum is not limited under 35 USC 156(g)(6)(A) which states that if the patent involved is issued after the date of enactment of this section, the period of extension may not exceed 5 years. The period of this extension is 1 year, 3 months and 4 days, which is less than 5 years.

f) Applicant herewith, claims an expiration date of 24 May 2008 for U.S. Patent 4,902,683 under 35 USC 156.

Given the complex and lengthy regulatory review period required for this new animal drug product, Applicant believes that the Length of Extension as determined in Scenario I above is the more appropriate period of extension for U.S. Patent 4,902,683.

The regulatory chronologies attached hereto show that Applicant put forth continuous, diligent effort throughout this drug's lengthy regulatory review. Also, this period of extension is most consistent with the legislative intent of 35 USC 156 which is to encourage new drug research by restoring the patent term lost to premarket approval. Clearly, Applicant believes that the Length of Extension as determined in Scenario II above is the minimum period of extension to which U.S. Patent 4,902,683 is entitled.

13. **Acknowledgment of Duty of Disclosure**

Applicant acknowledges a duty to disclose to the Commissioner of Patents and Trademarks and the Secretary of Health and Human Services any information which is material to the determination of entitlement to the extension herein sought. No such information beyond what is disclosed herein is known to Applicant.

14. **Fee**

The prescribed fee for receiving and acting upon this application for extension to be charged to the applicant's account as authorized in the accompanying letter which is submitted in duplicate.

15. **The Name, Address and Telephone Number of the Person to Whom Inquiries and Correspondence Relating to the Application for Patent Term Extension Are to Be Directed**:

Martha A. Gammill
Intellectual Property Legal Services
Pharmacia & Upjohn
301 Henrietta St.
Kalamazoo, MI 49001
Telephone: 616-833-7829

or

Lawrence T. Welch
Intellectual Property Legal Services
Pharmacia & Upjohn
301 Henrietta St.
Kalamazoo, MI 49001
Telephone: 616-833-9537

16. **Certified Duplicate of Application**

A certified duplicate of this application is attached as "Appendix E."

17. **Declaration**

The declaration set forth in 37 CFR 1.740 (b) for Patent Term Extension under 35 USC 156 is attached as "Appendix D."

Signed this 24th day of June, 1996.

Martha A. Gammill

Martha A. Gammill, Attorney
Registration No. 31,820
Telephone: (616) 833-7829

APPENDIX A-1

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re : U.S. Patent 4,902,683
Issued : 20 February 1990
To : Pharmacia & Upjohn Company (formerly The Upjohn Company)
For : CRYSTALLINE CEPHALOSPORIN HYDROHALIDE SALTS

Commissioner of Patents and Trademarks
Box Patent Extension
Washington, DC 20231

POWER OF ATTORNEY

Pharmacia and Upjohn Company, a corporation organized and existing under the laws of Delaware and having its head office at 7000 Portage Road, Kalamazoo, Michigan 49001 (formerly known as The Upjohn Company), being the owner of record of the above-identified U.S. Letters Patent, hereby appoint Raymond G. Arner (Registration 32,958), Donald L. Corneglio (Registration 30,741), James D. Darnley, Jr. (Registration No. 33,673), Martha A. Gammill (Registration No. 31,820), William G. Jameson (Registration No. 27,199), Bruce Stein (Registration No. 27,231), Lawrence T. Welch (Registration No. 29,487), Thomas A. Wootton (Registration No. 35,004), and Lucy X. Yang (Registration No. 40,259), all registered to practice before the Patent and Trademark Office as my attorneys or agents with full power of substitution and revocation to prosecute this application and all divisions and continuations thereof and to transact all business in the Patent and Trademark Office connected therewith and request that all correspondence and telephone communications be directed to the following person(s) at the mailing address and telephone number hereafter given:

Name	:	Martha A. Gammill, Attorney
Registration No.	:	31,820
Address	:	Intellectual Property Legal Services Pharmacia & Upjohn 301 Henrietta Street Kalamazoo, Michigan 49001
Telephone No.	:	(616) 833-7829 or (616) 833-9500
Telefax No.	:	(616) 833-8897 or (616) 833-2316

PHARMACIA & UPJOHN COMPANY

By: _____
Raymond G. Arner, Esq.
Vice President, Intellectual Property Legal Services

Dated: 24 June 1996

APPENDIX A-2

Appendix A-2 is a copy of the Certificate of Amendment showing the name change from The Upjohn Company to Pharmacia & Upjohn Company

State of Delaware

Office of the Secretary of State

I, EDWARD J. FREEL, SECRETARY OF STATE OF THE STATE OF DELAWARE, DO HEREBY CERTIFY THE ATTACHED IS A TRUE AND CORRECT COPY OF THE CERTIFICATE OF AMENDMENT OF "THE UPJOHN COMPANY", CHANGING ITS NAME FROM "THE UPJOHN COMPANY" TO "PHARMACIA & UPJOHN COMPANY", FILED IN THIS OFFICE ON THE ELEVENTH DAY OF JUNE, A.D. 1996, AT 3:30 O'CLOCK P.M.

Edward J. Freel, Secretary of State

0527510 8100

960170705

AUTHENTICATION: 7982329

DATE: 06-12-96

CERTIFICATE OF AMENDMENT

OF

CERTIFICATE OF INCORPORATION

OF

THE UPJOHN COMPANY

The Upjohn Company, a Delaware corporation, hereby certifies as follows:

FIRST. The Board of Directors of said corporation duly adopted a resolution setting forth and declaring advisable the amendment of Article First of the certificate of incorporation of said corporation so that, as amended, said Article shall read as follows:

"FIRST. The name of the corporation is Pharmacia & Upjohn Company (the "Corporation")."

SECOND. In lieu of a vote of stockholders, written consent to the foregoing amendment has been given by the holder of all of the outstanding stock entitled to vote thereon in accordance with the provisions of Section 228 of the General Corporation Law of the State of Delaware; and such amendment has been duly adopted in accordance with the provisions of Section 242 of the General Corporation Law of the State of Delaware.

IN WITNESS WHEREOF, The Upjohn Company has caused this certificate to be signed by Don W. Schmitz, its Vice President, Corporate Law, and Assistant Corporate Secretary, on the 31st day of June, 1996.

THE UPJOHN COMPANY

By: Don W. Schmitz

Don W. Schmitz
Vice President, Corporate Law, and
Assistant Corporate Secretary

APPENDIX B

Appendix B is a true copy of U.S. Patent No. 4,902,683

United States Patent [19]

Amin et al.

[11] **Patent Number: 4,902,683**

[45] **Date of Patent: Feb. 20, 1990**

[54] **CRYSTALLINE CEPHALOSPORIN HYDROHALIDE SALTS**

[75] Inventors: **Mahendra I. Amin, Kalamazoo; Jay A. Campbell, Portage, both of Mich.**

[73] Assignee: **The Upjohn Company, Kalamazoo, Mich.**

[21] Appl. No.: **312,401**

[22] Filed: **Feb. 17, 1989**

Related U.S. Application Data

[63] Continuation of Ser. No. 898,676, Aug. 21, 1986, abandoned, which is a continuation of Ser. No. 664,651, Oct. 25, 1984, abandoned.

[51] Int. Cl.[4] C07D 501/36; A61K 31/545
[52] U.S. Cl. 514/206; 540/227
[58] Field of Search 540/227; 514/206

[56] **References Cited**

U.S. PATENT DOCUMENTS

4,464,367 8/1984 Labeeuw et al. 540/227

FOREIGN PATENT DOCUMENTS

2036746A 7/1980 United Kingdom .

Primary Examiner—Nicholas S. Rizzo
Attorney, Agent, or Firm—Martha A. Cox

[57] **ABSTRACT**

Crystalline hydrohalide salts of the cephalosporin antibiotic ceftiofur, processes for their manufacture, and pharmaceutical compositions containing one of these salts are provided.

13 Claims, No Drawings

APPENDIX C

Appendix C is a chronological listing of the activity and submissions under INADs 4601 and 9138 and NADA 140-890

To FDA	From FDA	Miscellaneous	Date	Tab No.	Subject
Gable		Originally submitted to INADA 2882	8/29/85	(1)	Upjohn submits amendment to INADA 2882 to include the use of the ceftiofur hydrochloride salt (U-64,279A) for treatment of bovine respiratory disease.
Gable		Originally submitted to INADA 2882	9/24/85	(2)	Upjohn requests conference to discuss the overall development plan to compare therapeutic equivalence between the ceftiofur sodium (U-64,279E) and ceftiofur HCl salt formulations.
	O'Haro		12/12/85	(3)	(Re: 1) FDA assigns INADA #4601 for this application.
Norcross		Authorization	12/26/85	(4)	(Re: 1) FDA authorizes the treatment of 2000 cattle with the hydrochloride salt of ceftiofur intramuscularly at a dose rate up to 4.4 mg/kg body weight daily for up to five days and requests copy of investigational label.
Gable		Hand carried by CJF	1/16/86	(5)	Upjohn submits data (TR 788-9760-85-009) which supports use of calves to study metabolism of ceftiofur in all cattle, and also requests that for future metabolism studies, weaned calves may be used & considered to be valid predictors of metabolism in cattle per se.
	Haines		1/21/86	(6)	(Re: 2) FDA comments on human food safety regarding comparison of HCl formulation with sodium salt. Also requests submission of agenda (for proposed meeting) and results of sodium salt studies, & a summary of the pharmacokinetic and/or toxicological approach.
X			2/21/86	(7)	Drug shipment to Dallas P. Horton, D.V.M., Wellington, Colorado. Trial #788-9690-0-86-004. (Also under INAD 2882)
X			2/21/86	(8)	Drug shipment to David T. Bechtol, D.V.M., Canyon, Texas. Trial #788-9690-0-GGS-86-002. (Also under INAD 2882)

To FDA	From FDA	Miscellaneous	Date	Tab No.	Subject
X			2/21/86	(9)	Drug shipment to Alvin J. Edwards, Kansas State Univ., Manhattan, Kansas. Trial #788-9690-0-86-003.
x			2/21/86	(10)	Upjohn submits labels for investigational drug shipped under provisions of this INAD.
X			3/10/86	(11)	Drug shipment to David T. Bechtol, D.V.M., Agri-Research Center, Canyon, Texas. Trial #788-9690-0-GGS-86-002, 2nd shipment.
x			3/10/86	(12)	Drug shipment to Alvin J. Edwards, D.V.M., Ph.D., Kansas State Univ., Manhattan, Kansas, Trial #788-9690-0-GGS-86-003, 2nd shipment.
Gable			3/27/86	(13)	Upjohn submits memo of FDA/TUC telephone conference held 2/28/86 regarding selection of doses to be used in therapeutic equivalency study involving both HCl and NA salts.
Gable			5/2/86	(14)	Upjohn confirms Upjohn/CVM conference for May 8, 1986 to discuss activities in investigation of hypersensitivity potential of ceftiofur.
	McRae for Haines		5/7/86	(15)	(Re: 5) FDA comments regarding data contained in TR #788-9760-85-009 and offers comments concerning human food safety. Upjohn has not addressed the following 1) metabolism of compound in regard to fragmentation or cleavage of the molecule 2) similarity of disposition of sodium and HCl salts of ceftiofur.
	Haines		5/19/86	(16)	(Re: 13) FDA has no adverse comments regarding TUC's interpretation of conference of 2/28/86 relative to dose selection. Proceed with study substituting 0.5 mg/lb/day dose level as discussed.

To FDA	From FDA	Miscellaneous	Date	Tab No.	Subject
Gable		Via GBooze	7/24/86	(17)	(Re: 2) Upjohn proposes to conduct an additional dose finding study. Also submits preliminary analysis of data for multi-location therapeutic equivalence study conducted in feedlot animals with BRD.
			8/12/86	(18)	Drug shipment to The Upjohn Research Farm, Trial No. 788-9690-I-GGS-86-006, 80 vials, 10 ml (1,000 mg) of Ceftiofur.
Gable			9/23/86	(19)	Upjohn submits notice of shipment of drug to the United Kingdom. The drug will be labeled and used in a manner consistent with local legal requirements of Holland and Ireland.
	Haines		10/27/86	(20)	(Re: 17) FDA finds plans for dose finding and multi-location studies acceptable. However, comments regarding the .5 mg/lb body weight dose stating the results do not support the previously collected data. Difference may be due to duration of the dose.
			11/6/86	(21)	Drug shipment to David T. Bechtol, D.V.M., Canyon, Texas. Trial #788-9690-0-GGS-86-008.
			11/6/86	(22)	Drug shipment to Clarence G. Sitzman, D.V.M., Horton Feedlot & Research Center, Wellington, Colorado. Trial #788-9690-0-GGS-86-009.
			11/6/86	(23)	Drug shipment to Daryl G. Meyer, D.V.M., Gothenberg, Nebraska. Trial #788-9690-0-GGS-86-010.
			11/6/86	(24)	Drug shipment to Robert A. Smith, D.V.M., Stillwater, Oklahoma. Trial #788-9690-0-GGS-86-011.

To FDA	From FDA	Miscellaneous	Date	Tab No.	Subject
HHS			11/25/86	25	Drug shipment to Dr. Daryl G. Meyer of Gothenberg, Nebraska. Trial #788-9690-0-GGS-010 (2nd shipment).
HHS			11/25/86	26	Drug shipment to Dr. Robert A. Smith of Stillwater, Oklahoma. Trial #788-9690-0-GGS-86-011 (2nd shipment).
Haines		Hand carried-CJF ***Filmed 1/5/87***	12/5/86	27	(Re: 20) Upjohn submits TR#788-9690-86-002 as response to FDA's question regarding the mortality rate experienced with the 0.5 mg/lb body weight dose of ceftiofur Na in the therapeutic equivalency study.
	Haines		3/3/87	28	(Re: 27) Because the majority of the animals in the field trials required a 5-day regimen of 0.5 mg/lb body weight, and were medicated only for 3 days, CVM recommends the label indicate treatment regimen for "up to 5 days".
Gable		Hand carried-CJF	2/10/88	29	Based on several stated facts, Upjohn requests preslaughter withdrawal period be reduced from 90 days to 14 days.
	Carnevale	AMENDED AUTHORIZATION	2/29/88	30	(Re: 29) CVM concurs with request to reduce withdrawal period from 90 days to 14 days.
Vaughn		See NADA 140-890	3/5/93	31	**Revised formulation**-Upjohn provides information on the revised formulation of ceftiofur HCl, and the validation of gamma irradiation terminal sterilization procedures, and other general information relative to this application.
Vaughn			3/9/93	32	**Revised formulation-Protocol submitted**-Upjohn submits proposed pivotal study protocol, 788-9690-I-SAB-93-001. Referenced studies (previously submitted) included. Study to establish revised formulation is equally bioequivalent to approved ceftiofur Na. Requests conference to discuss proposed study (continued from Vol 2).

To FDA	From FDA	Miscellaneous	Date	Tab No.	Subject
Vaughn			3/9/93	32	**Revised formulation**-Upjohn submits and requests review of proposed pivotal study protocol, 788-9690-I-SAB-93-001. Referenced studies (previously submitted) included. Study to establish revised formulation is equally bioequivalent to approved ceftiofur Na. Requests conference at earliest convenience to discuss proposed study (continued in Volume 1).
Vaughn		Refer also to NADA 140-890	3/23/93	33	(Re: 31) **Revised formulation**- Per phone request, Upjohn amends submission of 3/5/93 to reflect it now be phase-reviewed under INAD 4601 as a manufacturing section.
Vaughn		Refer also NADA 140-890	4/5/93	34	(Re: 32) **Developmental plans** -Upjohn requests confirmation of a meeting for 4/14/93 to discuss various developmental plans.
Vaughn			5/4/93	35	(Re: 32,34) **Developmental plans** - TUC requests meeting for 12 May 1993 to further discuss developmental plans. Attachments submitted via facsimile; not formally submitted.
Vaughn			6/10/93	36	(Re: 34) Upjohn submits four Tech Reports and requests these be reviewed within the context of the developmental proposal agreed to at the 5/12/93 conference (continued from Volume 3).

To FDA	From FDA	Miscellaneous	Date	Tab No.	Subject
Vaughn			6/10/93	36	(Re: 34) Upjohn submits four Tech Reports and requests these be reviewed within the context of the developmental proposal agreed to at the 5/12/93 conference (continued in Volume 2).
	Vaughn	F-0022	6/21/93	37	(Re: 32,35) **Protocol review**-FDA offers detailed comments on protocol submitted 3/9/93. Dose Determination and Residue Decline study will be required. Results of dose determination study must meet stated criteria. Submit protocol.
Vaughn			6/25/93	38	(Re: 4,30,34) **Amendment to INAD** -Upjohn amends INAD to provide for 2000 additional beef, for IM or SC administration, 48 hr meat withdrawal time, and a 24 hr milk discard.
Vaughn			6/30/93	39	**Dose Confirmation Protocol** -Upjohn submits the proposed pivotal dose confirmation protocol, 788-9690-0-BH-93-001.
Vaughn			7/28/93	40	(Re: 34,35) **MOC**-Upjohn submits Memo of Conferences held 14 and 21 April and 12 May 1993, concerning all remaining components of the development plan needed to complete the NADA.
	Vaughn	E-0030	8/20/93	41	(Re: 39) **Dose Confirmation Protocol** - FDA finds protocol well designed & approprate for efficacy evaluation; however, a few procedural statements need clarification. Requests submission of revised protocol.
	Vaughn	Y-0031	9/9/93	42	(Re: 40) **MOC of 5/12** - CVM reviews agreements reached regarding project plans toward approval of product; specifically, efficacy, target animal safety, and tissue and milk residue studies.
Vaughn			9/27/93	43	(Re: 37) **Revised protocol**- Upjohn submits Protocol 788-7926-I-SAB-93-003 (formerly 001), revised as per 5/12/93 meeting, and also includes some additional changes.

To FDA	From FDA	Miscellaneous	Date	Tab No.	Subject
Vaughn			9/30/93	44	(Re: 41) **Revised Dose Confirmation protocol-** Upjohn submits revised protocol 788-9690-0-BH-93-001 and includes list of all modifications.
Vaughn			9/30/93	45	(Re: 37,43) **Additional data-** Upjohn submits TR# 705-7923-93-005; 93-007; and 93-010 to document the MIC_{60} and MIC_{90} for each species listed on current labeling for Naxcel S. Po. and thus will be basis for Excenel S. Susp labeling.
	Livingston	**AMENDED AUTHORIZATION** D-0029	10/1/93	46	(Re: 38) **Amended authorization-** CVM authorizes 2000 additional animals, addition of subcutaneous route, a 48 hr pre-slaughter withdrawal, and a 48 hr milk discard time.
Vaughn			10/14/93	47	(Re: 40,42) **Pivotal Tissue Residue Protocol-** Upjohn submits protocol 788-7926-0-SAB-93-004. Upjohn refers CVM to the 9/28/93 and 9/9/93 submissions to assist in review.
	Vaughn	Y-0031	10/18/93	48	(Re: 32,35,40,42) **MOC of 4/14/ &5/12-** CVM cites some confusion in Upjohn summaries of the 4/14 and 5/12/93 meetings (submitted 7/28/93). CVM offers several additional comments which were inadvertently omitted in their response letter of 9/9/93.
HHS			10/19/93	49	Drug shipment to Dr. Terry Terhune, Health Management Services, Tulare, CA., Trial #788-9690-0-BH-93-002 (dose confirmation study).
	Haibel	Via fax	10/22/93	50	(Re: 41,43) **Dose Confirmation Procotocol** - Per CVM suggestions, Upjohn has contacted CVM (Dr. Nevius) regarding statistical-related questions 5 & 6 in CVM letter E0030. Upjohn now seeks confirmation that these issues are now resolved.

To FDA	From FDA	Miscellaneous	Date	Tab No.	Subject
Weber			11/5/93	51	(Re: 48) **Protocol-** As committed to in meeting of 4/14/93, Upjohn submits "Validation Protocol for Radiation Sterilization". Two other protocols will be submitted at a later date.
	Vaughn	E-0032	11/9/93	52	(Re: 32,35,43) **Revised Protocol-** CVM finds revised protocol acceptable.
	Vaughn	E-0333	11/15/93	53	(Re: 44) **Dose confirmation protocol-** CVM finds revised protocol acceptable.
	Vaughn	E-0035	11/29/93	54	(Re: 47) **Tissue Residue protocol-** CVM offers in-depth comments regarding study design.
HHS			11/30/93	55	Upjohn notifies FDA of shipment of 150, 100 ml vials of ceftiofur hydrochloride sterile suspension to Upjohn subsidiary in Belgium, c/o ANDeBock.
		E-mail-regarding CVM/TUC phone call	11/30/93	56	(Re: 51) **Validation Protocol for Radiation Sterilization-** CVM not satisfied with protocol and written response will not issue. Upjohn should submit proposed plans and request a conference.
		Marnane	12/3/93	57	(Re: 51) **Comments-Validation Protocol-**Protocol only contains generalized information; more specific information is necessary before validation protocols can be evaluated.
Haibel			12/13/93	58	(Re: 54) **Meeting-Tissue Residue Study-** Meeting requested to discuss injection site tissue collection procedure to be utilized; agenda enclosed.
Haibel			12/13/93	59	(Re: 51,56) **Meeting-Irradiation Ster. Protocol-** Meeting requested regarding issues concerning irradiation sterilization protocol; and to review TUC's approach to container closure integrity. Rationale and overview included.

To FDA	From FDA	Miscellaneous	Date	Tab No.	Subject
	Vaughn	P-0028	12/14/93	60	(Re: 36) **Tech Reports review**- Results of TR 788-9760-87-014, 788-9760-89-002 accepted. Method validation missing from TR 788-9760-88-014; review cannot be completed. Comments regarding TR 788-7926-91-006 need to be addressed before method is found to be acceptable.
Vaughn			1/26/94	61	(Re: 54,59) **MOC**- Upjohn submits Memo of teleconference regarding injection site collection procedures and regarding Item 4 of CVM's 11/29/93 letter. Also includes a trip report, and revised protocol 788-7926-0-SAB-93-004, and TR 7220-92-021.
	Vaughn	H-0034	1/27/94	62	(Re: 45) CVM completes review of submission and requests we submit the MIC's of reference strains and interpretative criteria for acceptance of test results.
Vaughn			3/9/94	63	**Meeting request**- Upjohn requests meeting to discuss Chemistry/Manufacturing/Control issues, specifically; revised formulation, specifications, manufacturing and nada timeline, pre-approval inspection, and revised EA.
	Vaughn	Y-0041	3/23/94	64	(Re: 61) CVM notes some discrepancies in Memo of Teleconference. Also comments on Trip Report, Injection Site Reactions, and Revised Tissue Residue Protocol (decision criteria for study incomplete, pending receipt of supporting documentation).
		Interoffice Memo (not submitted to CVM)	4/11/94	65	(Re: 59) Upjohn documents Upjohn/CVM meeting of 12/15/93 discussing 1) validation of radiation process used to terminally sterilize SOS ceftiofur HCl and 2) container closure integrity test.

To FDA	From FDA	Miscellaneous	Date	Tab No.	Subject
Vaughn			4/25/94	66	(Re: 62) Upjohn responds to questions raised in CVM's letter of 1/27/94 relative to MIC data. Data requested only available from Sensititre so Upjohn provides data generated in labs of Dr. Thornsberry and Upjohn.
Vaughn			4/26/94	67	(Re: 63) Upjohn submits MOC of meeting held 3/31/94 regarding proposed submission of a NADA for revisesd formulation of ceftiofur HCl sterile susp.
	Vaughn	Y-0044	5/23/94	68	(Re: 67) CVM finds meeting minutes of 3/31/93, submitted 4/26/94, satisfactory. CVM also provides its minutes of the meeting. Notes meeting was held 3/30/94, not 3/31/94.
	Vaughn	G-0043	6/27/94	69	(Re: 45,62,66) FDA determines that issues concerning MIC's of reference strains have been adequately addressed.
HHS			3/20/95	70	Drug shipment to Dr. Scott A Brown, Upjohn. Trial #788-7926-I-SAB-95-001, pharmacokinetic study. Protocol and investigational labeling included.

To FDA	From FDA	Miscellaneous	Date	Tab No.	Subject
Haibel			4/11/95	71	(Re: 70) Teleconference requested to discuss and obtain CVM's guidance concerning protocol deviation encountered during study (protocol 788-7926-I-SAB-95-001, GLP Study 95-072).
Haibel			4/14/95	72	(Re: 71) Modification to protocol is acceptable; TUC agrees to prepare deviation to be incorporated into study file.
	Vaughn	Z-0046& Y-0047	5/15/95	73	(Re: 70,71) CVM determines submissions accurately reflect what was discussed and agreed upon.
Weber		cc: courtesy copy to Vaughn, Friedlander	5/24/95	74	(Re: 36,60) In response to CVM comments of 12/14/93, TUC provides additional lab notebook pages (788-9760-88-014); and a revised milk method.
HHS			7/31/95	75	Drug shipment to EJRobb, DVM, 9691-90-40, TUC. Trial #788-9690-O-EJR-95-002A, Lockshore Farms, Delton, MI. Protocol 788-9690-O-EJR-95-002 included (milk-residue study).
Mulligan		Also indexed in NADA 140-338, INAD 8894&9138	9/20/95	76	(Re: 63) Upjohn submits MOC of meeting held 8/9/95 to discuss CVM's current position on EA requirements & TUC's proposals for revising and completing EA's for several applications.
	Mulligan	Same as above Y0050	11/8/95	77	(Re: 76) CVM reviews MOC and agrees with contents except items under Example 5.
	Weber	P-0048	1/3/96	78	(Re: 36,60,74) FDA provides in-depth comments regarding 4 Tech Reports submitted. Residue stability issue not resolved. Insufficient data provided.

Communication: CEFTIOFUR HYDROCHLORIDE (Bacterial Resp. Disease-Swine) INAD 9138 Volume 1, Page 1

To FDA	From FDA	Miscellaneous	Date	Tab No.	Subject
Vaughn			11/5/93	1	Upjohn proposes a new INAD be established for the hydrochloride salt of ceftiofur as antimicrobial therapy for swine. Requests authorization for 5000 swine, 3 IM doses once daily, not to exceed 5 mg/kg BW, and a 10-day withdrawal period. (INAD 6067 to be retained exclusively for ceftiofur Na for bacterial respiratory disease and colibacillosis in swine).
	Henry		11/10/93	2	(Re: 1) FDA acknowledges receipt of and assigns No. 9138 to this application.
HHS			11/30/93	3	**Drug shipment**- Upjohn submits notice of drug shipment of 150 ml vials of ceftiofur HCl sterile suspension to the subsidiary in Belgium, c/o ANDeBock.
	Livingston	**AUTHORIZATION** A-0000	3/1/94	4	(Re: 1) FDA grants authorization as requested (5000 swine, IM once daily for 3 days, 5 mg/kg BW, 10-day withdrawal period).
	Livingston	A-0000	3/1/94	5	(Re: 1,4) To facilitate future reviews, product formulation should be clearly identified. As requested, this INAD is categorically excluded from requirement to prepare an EA.
Vaughn			3/15/94	6	Upjohn details proposal designed to support the approval of a supplemental application to unapproved NADA 140-890 to include treatment of the bacterial component of respiratory disease in swine.
Vaughn			5/5/94	7	(Re: 6) Upjohn submits request and agenda for meeting (via telephone) to be held 5/24/94 to discuss and reach concurrence on Upjohn's development plan.
Vaughn			6/1/94	8	(Re: 6,7) Upjohn expresses grave concerns about teleconference of 5/24/94 because Upjohn was informed that the efficacy portion could not be discussed because of various concerns by Agency personnel. Upjohn requests CVM reconsider its position.

To FDA	From FDA	Miscellaneous	Date	Tab No.	Subject
Vaughn			6/28/94	9	(Re: 6,7) Upjohn submits MOC of 5/24/94 relative to reaching concurrence on TUC's development plan for generating pivotal data.
Vaughn			7/15/94	10	(Re: 6,7,8,9) Upjohn confirms meeting for 7/27/94 to discuss and gain CVM concurrence on the efficacy component of the development plan.
Vaughn			8/18/94	11	(Re: 10) Upjohn provides Memorandum of the 7/27/94 Conference held to review and reach concurrence on the efficacy requirements for an NADA.
	Vaughn	Y-0005	8/19/94	12	(Re: 8,9) Upjohn's MOC accurately reflect content of 5/24/94 meeting, however FDA includes additional info in their MOC. Offers comments regarding Manufacturing Chemistry; EA; TAS; Efficacy & Pharmacokinetics and Human Food Safety.
	Vaughn	Y-0007	10/17/94	13	(Re: 11) Per CVM, Upjohn's MOC submitted 8/18/94 accurately reflects contents of meeting. CVM offers additional comments on "efficacy", and "human food safety" and includes a copy their MOC of same.
Miller		Informally provided by facsimile	11/4/94	14	Upjohn provides "working samples" to illustrate questions concerning the new HFS tissue consumption factor guidelines. Will discuss at Mtg. 8 Nov., 1994.
Vaughn		**PHASED REVIEW-TAS**	3/2/95	15	**Phased Review**-Upjohn submits Target Animal Safety component. Includes supporting technical reports; labeling and FOI.

To FDA	From FDA	Miscellaneous	Date	Tab No.	Subject
Weber		**Phased Review-Human Food Safety**	3/2/95	16	**Phased Review-Upjohn submits the Human Food Safety component.** Begins in Volume 4, ends in Volume 2.

To FDA	From FDA	Miscellaneous	Date	Tab No.	Subject
Weber		**Phased Review-Human Food Safety**	3/2/95	16	**Phased Review-Upjohn submits the Human Food Safety component.** Begins in Volume 4, ends in Volume 2.

To FDA	From FDA	Miscellaneous	Date	Tab No.	Subject
Weber		**Phased Review- Human Food Safety**	3/2/95	16	**Phased Review-** Upjohn submits the Human Food Safety component. Included are supporting documents; labeling and FOI. Begins in Volume 4, ends in Volume 2.
Weber		**Phased Review- Efficacy**	3/2/95	17	**Phased Review-** Upjohn submits the Efficacy component. Included are supporting documents; labeling and FOI. Begins in Volume 9, ends in Volume 4.

To FDA	From FDA	Miscellaneous	Date	Tab No.	Subject
Weber		**Phased Review-Efficacy**	3/2/95	17	**Phased Review-** Upjohn submits the Efficacy component. Begins in Volume 9, ends in Volume 4.

To FDA	From FDA	Miscellaneous	Date	Tab No.	Subject
Weber		**Phased Review-Efficacy**	3/2/95	17	**Phased Review-** Upjohn submits the Efficacy component. Begins in Volume 9, ends in Volume 4.

To FDA	From FDA	Miscellaneous	Date	Tab No.	Subject
Weber		**Phased Review-Efficacy**	3/2/95	17	**Phased Review-** Upjohn submits the Efficacy component. Begins in Volume 9, ends in Volume 4.

To FDA	From FDA	Miscellaneous	Date	Tab No.	Subject
Weber		**Phased Review-Efficacy**	3/2/95	17	**Phased Review-** Upjohn submits the Efficacy component. Begins in Volume 9, ends in Volume 4.

To FDA	From FDA	Miscellaneous	Date	Tab No.	Subject
Weber		**Phased Review-Efficacy**	3/2/95	17	**Phased Review**- Upjohn submits the Efficacy components. Included are supporting technical reports and references; labeling, and the FOI. Begins in Volume 9, ends in Volume 4.
Jeang		**Informal communication via fax**	3/23/95	17a	**Phased Review**- Upjohn provides Dr. Jeang with listing of studies in swine target animal safety and efficacy phased review components.

To FDA	From FDA	Miscellaneous	Date	Tab No.	Subject
Mulligan		**Phased Review-EA**	3/28/95	18	**Phased Review**- Upjohn submits the Environmental Assessment document and supporting tech reports and references; labeling and FOI. Ends in Volume 10, begins in Volume 17.

To FDA	From FDA	Miscellaneous	Date	Tab No.	Subject
Mulligan		**Phased Review-EA**	3/28/95	18	**Phased Review**- Upjohn submits the Environmental Assessment document and supporting tech reports and references; labeling and FOI. Ends in Volume 10, begins in Volume 17.

To FDA	From FDA	Miscellaneous	Date	Tab No.	Subject
Mulligan		**Phased Review-EA**	3/28/95	18	**Phased Review**- Upjohn submits the Environmental Assessment document and supporting tech reports and references; labeling and FOI. Ends in Volume 10, begins in Volume 17.

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Mulligan		**Phased Review-EA**	3/28/95	18	**Phased Review**- Upjohn submits the Environmental Assessment document and supporting tech reports and references; labeling and FOI. Ends in Volume 10, begins in Volume 17.

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Mulligan		**Phased Review-EA**	3/28/95	18	**Phased Review**- Upjohn submits the Environmental Assessment document and supporting tech reports and references; labeling and FOI. Ends in Volume 10, begins in Volume 17.

To FDA	From FDA	Miscellaneous	Date	Tab No.	Subject
Mulligan		**Phased Review-EA**	3/28/95	18	**Phased Review**- Upjohn submits the Environmental Assessment document and supporting tech reports and references; labeling and FOI. Ends in Volume 10, begins in Volume 17.

To FDA	From FDA	Miscellaneous	Date	Tab No.	Subject
Mulligan		**Phased Review-EA**	3/28/95	18	**Phased Review**- Upjohn submits the Environmental Assessment document and supporting tech reports and references; labeling and FOI. Ends in Volume 10, begins in Volume 17.

To FDA	From FDA	Miscellaneous	Date	Tab No.	Subject
Mulligan		**Phased Review-EA**	3/28/95	18	**Phased Review**- Upjohn submits the Environmental Assessment document and supporting tech reports and references; labeling and FOI. Ends in Volume 10, begins in Volume 17.
Vaughn		**Phased Review-TAS,HFS,Eff.**	3/30/95	19	**FOI**-Upjohn provides diskette of the FOI Summary. An additional diskette containing a data summary and statistical analysis from TR-796-7926-94-001 will be submitted under separate cover.
Vaughn		Re: Phased Review-Efficacy	4/14/95	20	(Re: 17,19) As requested, Upjohn provides ASCII Format Computer Diskette(2), which contains raw data for 796-7926-94-001.
		Interoffice communication	4/25/95	21	(Re: 17) Per phone conversation, CVM requests dilution range used in TR 705-7923-93-007 and 93-010, and values for quality control organisms. Also cites poor copy quality. Upjohn will provide.
Vaughn		Phased Review-Efficacy (minor amendment)	5/5/95	22	(Re: 17,21) Upjohn provides dilution range and quality control information and corrected copies of "Table 5" from the two TR's cited in phone conversation. Also provides some additional quality control information.
Newkirk			6/2/95	23	Confirmation requested for 6/14/95 mtng to discuss and gain CVM concurrence on proposal to validate a product lot size range using same manufacturing equipment. TUC will design & submit protocol based on discussions. MOC will issue.
Mulligan		Phased Review (EA) (minor amendment)	6/12/95	24	(Re: 18) Corrected pages of Reference 10 in the EA are provided.
Newkirk			6/23/95	25	(Re: 23) Upjohn submits MOC of 14Jun95 meeting. CVM supports proposal if certain conditions are met. Suggests conferencing post-approval validation studies with District office. PAI triggered by filing of complete NADA and estimate of approval date.

To FDA	From FDA	Miscellaneous	Date	Tab No.	Subject
		Informal communication	7/13/95	26	Per telephone call, CVM notes possible error in labeling. Comparative bioavailability section doesn't agree with TR and FOI. Error confirmed; corrections will be submitted.
	Jeang	Informal communication/fax	7/14/95	27	(Re: 26) FDA provides outline of changes needed on the labeling and FOI Summary.
		Informal communication	7/16/95	28	(Re: 26,27) CVM/TUC Phone conference regarding Comparative bioavailability sections of FOI and labeling. Upjohn agrees to make changes; fax to CVM for concurrence; then submit formally.
	Newkirk	Y0009	7/20/95	29	(Re: 25) Meeting of minutes satisfactory. CVM provides copy of the CVM MOC of 14June95.
Jagannath		Referenced in NADA 140-338.	7/26/95	30	EA Issues- Upjohn requests confirmation of conference for 9Aug95 at CVM to review, in general, information included in EA reports for 140-338(sheep) and INAD 9138(swine). Agenda enclosed.
Hillary		To USDA	8/3/95	30a	(Re: 25) Upjohn (via MClasby) provides MOC14Jun95 mtng; draft of NADA composition page; and analytical data for susp. content uniformity from lot 41026.
Mulligan		Indexed in FDA General& NADA 140-338	8/7/95	31	(Re: 30) TUC requests confirmation of meeting for 9Aug95 to discuss and clarify CVM's current position on EA requirements. (Attachments include 26Jul95 ltr&agenda).
Vaughn		Airborne	8/14/95	32	(Re: 15-18,26-28) Upjohn provides Revised FOI, Revised FOI on diskette, and revised product labeling (insert).

To FDA	From FDA	Miscellaneous	Date	Tab No.	Subject
Weber		**Phased Review**	8/16/95	33	Upjohn submits the Manufacturing Mehods and Controls Technical Section for phased review. Included is draft labeling (insert); and Section 4 and Section 5. (Begins in Volume 19, ends in Volume 18.)

To FDA	From FDA	Miscellaneous	Date	Tab No.	Subject
Weber		Phased Review	8/16/95	33	Upjohn submits Manufacturing Methods and Controls Section (CMC) for Phased Review. Included are draft labeling (insert), and Sections 4 and 5. (Begins in Vol. 19 ends, in Volume 18.)
Vaughn		Phased Review-Efficacy	8/21/95	34	(Re: 32) TUC submits minor corrections/revisions to comparative bioavailability information. Also included are revised FOI (hard copy&diskette) and Product labeling.
	Weber	P0012	8/31/95	35	(Re: 16) HFS - CVM provides in-depth comments regarding technical reports submitted. Requests submission of raw data,; method reports; and validation, namely, oral bioavailability comparison study in rats.
	Vaughn	A-0000	9/12/95	36	(Re: 15) FDA considers TAS component COMPLETE. Requires revisions to package insert in "Animal Safety" and "Precaution" sections.
Mulligan			9/20/95	37	(Re: 30) MOC of meeting held 8/9/95 to discuss EA requirements for various applications.
Weber			9/22/95	38	(Re: 35) Confirmation of meeting with CVM for 10/5/95 regarding the incomplete letter of 8/31/95.

To FDA	From FDA	Miscellaneous	Date	Tab No.	Subject
	Vaughn	(A-0000)	10/16/95	39	(Re: 17, 34)) FDA considers the Efficacy component COMPLETE. FDA has further revised the FOI Summary submitted 8/21/95 and provides copy of General Information and Effectiveness sections.
	Mulligan	(A000 & M0001)	10/16/95	40	(Re: 18,24) FDA grants a categorical exlusion from the requirement to prepare an EA.
	Mulligan	Y0013	11/8/95	41	(Re: 37) FDA agrees with MOC exept for some items under "Example 5".
	Weber	Z0014	11/21/95	42	Re: 35&38) FDA provides MOC of 10/5/95 meeting . Requests Upjohn provide MOC of same.
Vaughn			1/8/96	43	(Re: 35) Upjohn responds to FDA's comments of 8/31/95 regarding Human Food Safety issues. Revised FOI & Labeling included. (Begins in Volume 24, ends in Vol. 20).

To FDA	From FDA	Miscellaneous	Date	Tab No.	Subject
Vaughn			1/8/96	43	(Re: 35) Upjohn responds to FDA's comments of 8/31/95 regarding Human Food Safety issues. Revised FOI & Labeling are included. (Begins in Vol. 24, ends in Vol. 20).

To FDA	From FDA	Miscellaneous	Date	Tab No.	Subject
Vaughn			1/8/96	43	(Re: 35) Upjohn responds to FDA's comments of 8/31/95 regarding Human Food Safety issues. Revised FOI & Labeling are included. (Begins in Vol. 24, ends in Vol. 20).

To FDA	From FDA	Miscellaneous	Date	Tab No.	Subject
Vaughn			1/8/96	43	(Re: 35) Upjohn responds to FDA's comments of 8/31/95 regarding Human Food Safety issues. Revised FOI & Labeling are included. (Begins in Vol. 24, ends in Vol. 20).

To FDA	From FDA	Miscellaneous	Date	Tab No.	Subject
Vaughn			1/8/96	43	(Re: 35) Upjohn responds to FDA's comments of 8/31/95 regarding Human Food Safety issues. Revised FOI & Labeling are included. (Begins in Vol. 24, ends in Vol. 20).
Vaughn			1/11/96	44	(Re: 43) Upjohn provides revised FOI via diskette as follow up to hard copy provided 1/8/96.
Newkirk			1/11/96	45	(Re: 33) Upjohn provides updated stability data (24 month expiry period) to be incorporated into the CMC section.
	Newkirk	P0011 (CMC)	1/23/96	46	(Re: 33) CVM incompletes CMC section. Seven specific areas are addressed including, labeling, finished product specs, HPLC Assay validation, sterility test validation, sterilization process validation, antimicrobial effectiveness testing, and stability.
		MOC-Informal communications	1/25/96	47	(Re: 46) Notes of teleconference held to discuss CVM's incomplete letter of 1/23/96. Response to incomplete should issue within 3 weeks.
Vaughn			1/31/96	48	Upjohn requests meeting (2/7/96) to discuss status of each phased review component. Agenda included.
Newkirk		Informal submission (not for DCU)	2/19/96	49	(Re: 46) Upjohn provides agenda for meeting to be held 2/22/96 to discuss CMC section. Proposed (draft) response to incomplete attached.
Leinback, Newkirk, Wong		Informal submission (not for DCU)	2/29/96	50	(Re: 46,47,48,49) Upjohn provides draft responses to questions raised by CVM-Upjohn teleconferences of 13,26&27Feb96 and meeting held 22Feb96.
Leinback, Newkirk, Wong		Informal submission (not for DCU)	3/5/96	51	(Re: 49) Upjohn provides overheads used during the 22Feb96 conference.
Newkirk			3/20/96	52	(Re: 46-51) Upjohn submits reponse to CVM incomplete letter of 1/23/96 relative to the CMC section. Six salient points addressed. Upjohn also requests implementation of PAI process. Revised labeling included.

To FDA	From FDA	Miscellaneous	Date	Tab No.	Subject
Haibel		Labeling	3/26/96	53	(Re: 52) Upjohn submits 9 copies of labeling components revised to delete references to "RTU", and some text formatting improvements.
Vaughn		Labeling	3/29/96	54	(Re: 53) Upjohn provides 9 copies of label, revised to add statement under Warnings section.
Vaughn		HFS-phased review	3/29/96	55	(Re: 35,43) Per FDA request, Upjohn provides minor amendment (per MBeconi-Barker) to HFS submission of 8Jan96.
Vaughn			3/29/96	56	Drug shipment to Dr. Jim Bradford, Upjohn Farms, for *In Vivo/In Vitro* syringeability assessment. Trial 796-9661-JRB-I-96-001.
		Phased Review Chemistry, Mfg/Control	4/2/96	57	(Re: 45,52) Chemistry, Manufacturing&Control conponent adequately addressed. Will consider component complete upon submission of revised vial label (storage statement) and a satisfactory cGMP inspection.
	Vaughn	Phased Review (HFS)	4/3/96	58	(Re: 43,52,54) Human Food Safety Component complete. Revised labeling acceptable. CVM further revises FOI; copy enclosed (w/Agency conclusions)
		Informal notice	4/4/96	59	Patent claiming ceftiofur hydrochloride per se (4,902,683) was granted 20 February 1990, expires 20 February 2007. Patent extension claim to be filed.
Keller			4/11/96	60	Drug shipment to Dr. S.A.Brown, Trial 796-7926-I-SAB-96-001, pharmacokinetic study.
	Holman		4/26/96	61	(Re: 57) Detroit District Office recommends approval based on satisfactory cGMP inspection.

COMMUNICATION EXCENEL (Sterile Suspension) NADA Volume 1, page 1

To FDA	From FDA	Miscellaneous	Date	Tab No.	Subject
Gable			3/30/88 MICROFILMED ON 4·5 87	(1)	Upjohn submits New Animal Drug Application to provide for the use of Ceftiofur HCL S. suspension for treatment of bovine respiratory disease. (Continued from Vol. 2)

To FDA	From FDA	Miscellaneous	Date	Tab No.	Subject
Gable			3/30/88 MICROFILMED ON 4-5-89	(1)	Upjohn submits New Animal Drug Application to provide for the use of Ceftiofur HCL S. suspension for treatment of bovine respiratory disease. (continued from Vol. 3)

COMMUNICATION EXCENEL (Sterile Suspension) NADA Volume 3, page 1

To FDA	From FDA	Miscellaneous	Date	Tab No.	Subject
Gable			3/30/88 MICROFILMED ON 4-5-89	(1)	Upjohn submits New Animal Drug Application to provide for the use of Ceftiofur HCL S. suspension for treatment of bovine respiratory disease. (continued from Vol. 4)

COMMUNICATION EXCENEL (Sterile Suspension) NADA Volume 4, page 1

To FDA	From FDA	Miscellaneous	Date	Tab No.	Subject
Gable			3/30/88	(1)	Upjohn submits New Animal Drug Application to provide for the use of Ceftiofur HCL S. Suspension for treatment of bovine respiratory disease. (continued from Vol. 5)

To FDA	From FDA	Miscellaneous	Date	Tab No.	Subject
Gable			3/30/88	(1)	Upjohn submits New Animal Drug Application to provide for the use of Ceftiofur HCL S. Suspension for treatment of bovine respiratory disease. (continued in Vol. 4)
	Christensen		4/5/88	(2)	(Re: 1) FDA acknowledges receipt of 3/30 submission and assigns NADA #140-890 to this application.
Gable		See also DMF5173, Vol. 1, T-4.	8/22/88	(3)	Upjohn provides explanation for an apparent discrepancy between the potency values for lots as reported in the NADA vs. those in the DMF. Corrected Table I and II also provided.
	Gable		10/28/88	(4)	(Re: 1) FDA incompletes application. Offers comments on "complete" sections (Human Food Safety, Environmental, Target Animal Safety) and "Incomplete" sections (Chemistry, Labeling, Efficacy & FOI). A zero withdrawal period granted.
	Gable		12/1/88	(5)	(Re: 4) FDA clarifies letter of 10/28/88 relative to Efficacy (considered complete) and Labeling (suggests meeting to discuss Rx vs. OTC status).
Gable			1/11/89	(6)	(Re: 4,5) Upjohn responds to FDA's incomplete letters by addressing and submitting revisions to the following sections: 1) Chemistry, 2) Labeling, and 3) FOI Summary.
Guest			1/12/89	(7)	(Re:4,5) Upjohn requests meeting to address marketing status.
Gable			2/9/89	(8)	(Re: 4) Per FDA/TUC conference call Upjohn provides supplier specifications and the proposed spec page for Phospolipon 100-H.
			filmed	4/5/89	

To FDA	From FDA	Miscellaneous	Date	Tab No.	Subject
Talbot		See FDA General for letter of 11/23/88	2/24/89	(9)	Per FDA letter of 11/23/88, Upjohn submits patent & exclusivity info as directed by the Generic Animal Drug & Patent Term Restoration Act.
	Gable		3/22/89 filmed 4-5-89	(10)	(Re: 6,8) FDA offers additional comments on Chemistry, Labeling and FOI Summary. Some additional changes required.
	Gable		4/12/89	(11)	(Re: 6) FDA reconfirms their disfavor with the "Indications" section of proposed labeling; should be exactly as was basis for approval of Naxcel.
Gable			5/11/89	(12)	(Re: 10,11) Based on FDA's comments, Upjohn submits a Revised Stability Commitment, Revised Draft Labeling, and Revised FOI Summary.
	Gable		9/28/89	(13)	(Re: 12) Excenel now approvable. Submit final printed labeling and revised FOI Summary.
Gable			11/16/89	(14)	(Re: 13) Upjohn submits final printed labeling, and FOI Summary (all reference to rat blood level data eliminated).
Rollins		Informally submitted via Airborne	1/19/90	(15)	(Re: 13) Upjohn provides a revised FOI Summary which includes deletion of all references to the LD_{50} studies in the Toxicology section.
			MICROFILMED ON	6-6-90	

To FDA	From FDA	Miscellaneous	Date	Tab No.	Subject
Gable			3/22/90 Filmed 6-6-90	16	(Re: 1) Upjohn submits an Amendment which included labeling facsimiles, FOI, and TR 788-7922-89-001, which provides info about the sensitivities of several BRD pathogens to ceftiofur.
Gable			7/18/90	17	Per phone conversation of 7/12/90, Upjohn submits revised EA which covers OTC use for treatment of BRD.
Kollath		Via airborne-informally submitted	8/3/90	18	Upjohn provides copies of labeling containing changes agreed upon 8/2/90. FDA will replace appropriate pages in existing documents.
Kollath		Informally submitted	10/18/90	19	Upjohn provides 5 copies of the revised (as per discussion of 10/17) FOI Summary and 9 copies of final printed labeling.
Kollath		Informally submitted	4/15/91	20	Upjohn provides nine copies of the revised FOI Summary changes as requested.
Kollath		Informally submitted	5/6/91	21	Upjohn provides 9 copies of the revised FOI Summary to complete the final approval package.
	Beaulieu		3/31/92	22	(Re: 5,7) Product should bear same dose range as Naxcel S. Po. (0.5 to 1.0 mg/lb). FDA concludes Excenel S. Susp. should be an Rx product and revised labeling must be submitted.
Beaulieu			4/10/92 Filmed 5-12-92	23	(Re: 22) Upjohn requests meeting discuss current CVM position and attempt to understand its rationale, justification and scope.

To FDA	From FDA	Miscellaneous	Date	Tab No.	Subject
Beaulieu			6/5/92	24	Upjohn confirms meeting for 11 June 1992 to discuss final outstanding issues associated with pending approvals including Rx labeling for this product.
Beaulieu			6/11/92	25	(Re: 23) Upjohn submits Memo of Conference concerning marketing status (OTC to Rx). Copy of regulatory chronology included.
Beaulieu			6/11/92	26	(Re: 21) Upjohn submits revised FOI which reflects the evaluation of the mutagenicity data, the marketing status and dose range.
Beaulieu		cc: Detroit District Office	6/26/92	27	Upjohn informs CVM that we are not presently prepared for a Pre-Approval Inspection (PAI). We will amend application when designated facility is available. Requests concurrence that NADA is approvable except for outstanding PAI concerns.
Beaulieu			6/30/92	28	(Re: 13,22) Upjohn submits revised labeling reflecting an Rx marketing status and provides for a dosage range so the "Indications" are exactly same as was basis for approval of Naxcel S. Po.
Guest		Faxed-not formally submitted	7/16/92	29	Upjohn confirms meeting to discuss a number of pending applications and wishes to review the history and current status relative to an approval of this NADA.
	Beaulieu		8/20/92	30	(Re: 26) CVM finds that Memo of Conference accurately interprets meeting. However, offers two comments regarding some of our remarks.
	Beaulieu	(E-005)	9/29/92	31	(Re: 27) Pending complete update of Manufacturing Chemistry portion, application remains incomplete. Will hold FOI & labeling in file for review at time of reactivation of NADA. Data must be provided to demonstrate that new formulation is bioequivalent to currently approved ceftiofur sodium product.

To FDA	From FDA	Miscellaneous	Date	Tab No.	Subject
Beaulieu		(E-005)	11/3/92	32	(Re: 31) Meeting of 7/29/92 briefly reviewed. New revised formulation to be presented within approx. 90 days. Each CVM comment in letter of 9/29/92 addressed. Upjohn seeks commitment that application may be approved pending review & acceptance of herein stated proposal relative to formulation change.
Vaughn			3/5/93	33	(Re: 31,32) Upjohn provides information on the revised formulation of ceftiofur HCl, and the validation of gamma irradiation terminal sterilization procedures, and other general information relative to this application.
Vaughn			3/8/93	34	(Re: 31,32) Upjohn proposes the establishment of equal bioavailability and thus bioequivalence based on demonstrating equal derivatized ceftiofur concentrations in plasma and lung following administration of ceftiofur HCl administered s.c. and ceftiofur Na administered i.m. Upjohn requests meeting to discuss proposal.
Vaughn			3/23/93	35	(Re: 33) Per FDA request, Upjohn amends submission to reflect it now be phase-reviewed under INAD 4601 as a manufacturing section, to facilitate CVM review under the "STARS" tracking system.
Vaughn			4/5/93	36	(Re: 34) Upjohn requests confirmation of meeting for 4/14/93 to discuss various aspects of this application.
Livingston		Also in NADA 140-338, Naxcel S. Po.	4/12/93	37	Upjohn requests confirmation of meeting for 21 April 1993 for a ceftiofur scientific overview.
Weber		from: Isomedix to: CVM	10/5/93	38	Isomedix authorizes FDA to refer to DMF #6501 for information in submissions by Upjohn for cobalt-60 radiation sterilization of Excenel S. Susp., at Isomedix.

To FDA	From FDA	Miscellaneous	Date	Tab No.	Subject
Vaughn		**Administrative NADA**	4/3/96	39	(Re: 31) Upjohn submits reactivation of this NADA . All requirements fulfilled by phased review submissions under INAD 9138. Approval for use in swine requested.
Vaughn		Also in INAD 9138 Informal info	4/4/96	40	Patent Info: patent claiming ceftiofur hydrochloride (4,902,683) was granted 20Feb90 and expires on 20Feb2007. Intent is to file for patent extension (within 60 days) when approval of NADA is received.
Vaughn			4/8/96	41	(Re: 39) Upjohn provides additional information to complete Section 4 (Mfg. Methods&Controls).
	Sundloff	NADA APPROVAL	4/26/96	42	(Re: 39,41) Application is approved. Notice being forwarded to Federal Register. Minor revision required for package insert (removal of 3 organisms). Marketing may begin as soon as final printed labeling is submitted.
Sundloff			5/13/96	43	(Re: 42) Upjohn commends CVM on its performance relative to the review & approval of this NADA.
Vaughn			5/15/96	44	(Re: 42) Upjohn provides 9 copies of revised final printed labeling to fulfill request of 26Apr96.
		Informal memo (SFSutherland/ DLKiefer)	5/17/96	45	Information providing verification of suspension samples (50-100 mL) of lot 41,033 being sent to the FDA District Office as forensic samples.

APPENDIX D

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re : U.S. Patent 4,902,683
Issued : 20 February 1990
To : Pharmacia & Upjohn Company (formerly The Upjohn Company)
For : CRYSTALLINE CEPHALOSPORIN HYDROHALIDE SALTS

Commissioner of Patents and Trademarks
Box Patent Extension
Washington, DC 20231

DECLARATION

Sir:

The undersigned attorney, an employee of Pharmacia & Upjohn Company, which is the Applicant (owner) for Extension of Patent Term under 35 USC 156 with regard to U.S. Patent 4,902,683, hereby declares as follows:

1. THAT she is a patent attorney authorized to practice before the patent and Trademark Office and has general authority from the owner to act on behalf of the owner in this patent matter;

2. THAT she has reviewed and understands the contents of the application being submitted pursuant to 35 USC 156 and 37 CFR 1.740;

3. THAT she believes the patent is subject to extension pursuant to 35 USC 156 and 37 CFR 1.710;

4. THAT she believes an extension of the length claimed is fully justified under 35 USC 156 and the applicable regulations; and

5. THAT she believes the patent for which the extension is being sought meets the conditions for extension of the term of patent as set forth in 35 USC 156 and 37 CFR 1.720.

The understood hereby declares further that all statements made herein of her own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the

knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any extension of patent term issuing thereon.

Further declarant sayeth not.

Signed this 24th day of June, 1996.

Martha A. Gammill

Martha A. Gammill, Attorney
Registration No. 31,820
Telephone: (616) 833-7829

APPENDIX E

I hereby certify that Appendix E, attached hereto, is a true copy of the application for patent term extension of U.S. Patent 4,902,683.

Date 24 June 1996

Martha A. Gammill

Martha A. Gammill, Attorney
Registration No. 31,820
Telephone: (616) 833-7829

PATENT/Docket No. 4121.JF1
U.S. Patent 4,902,683

CERTIFICATE OF MAILING (37 CFR 1.10)
"Express Mail" No.: TB689488536 US **Date of Deposit:** June 24, 1996

I hereby certify that this transmittal together with the patent application referred to below is being deposited with the United States Postal Service "Express Mail Post Office to Addressee" service under 37 CFR 1.10 on the date indicated above and is addressed to the Commissioner of Patents and Trademarks, Washington, DC 20231.

Julie Lyons, Legal Technician
Name of Person Mailing Paper

Julie Lyons
Signature

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Commissioner of Patents and Trademarks
Washington, DC 20231

Transmitted herewith for filing is the complete application for Patent Term Extension of United States Patent 4,902,683.

The filing fee is $1,060.00.

SPECIFIC DEPOSIT ACCOUNT AUTHORIZATION. Please charge my Deposit Account No. **21-0718** in the amount of the total filing fee above, or such greater or lesser amount as the Commissioner determines is required by law.

Respectfully submitted,

Date: 24 June 1996

Martha A. Gammill

Martha A. Gammill, Attorney
Registration No. 31,820
Telephone: (616) 385-7829

Mlg. Address: Intellectual Property Legal Services, Pharmacia & Upjohn Company, Kalamazoo, MI 49001

DEPOSIT COPY

II. FILING FEES

The filing fee has been calculated as shown below for the claims pending after amendment:

	No. Filed	No. Extra	Rate	Fee
TOTAL CLAIMS FEE	13 - 20 =	0	x $12	$0.00
INDEPENDENT CLAIMS FEE	2 - 3 =	0	x $34	$0.00
[] MULTIPLE DEPENDENT CLAIM FEE			$110	$0.00
BASIC FEE				$340.00
TOTAL FILING FEE				$340.00

SPECIFIC DEPOSIT ACCOUNT AUTHORIZATION. Please charge my Deposit Account No. 21-0718 in the amount of the total filing fee above. Triplicate copies of this paper are enclosed.

GENERAL DEPOSIT ACCOUNT AUTHORIZATION. The Commissioner is hereby authorized to charge payment of the following fees associated with this communication or during the pendency of this application or credit any overpayment to Deposit Account No. 21-0718:

(1) Any additional filing fees or fees for the presentation of additional claims required under 37 CFR 1.16.

(2) Any patent application processing fees under 37 CFR 1.17.

No authorization is given to charge the Issue Fee (37 CFR 1.18).

PATENT/Docket No. 4121.JF1
U.S. Patent 4,902,683

CERTIFICATE OF MAILING (37 CFR 1.10)
"Express Mail" No.: TB689488536 US **Date of Deposit:** June 24, 1996

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Julie Lyons, Legal Technician — Julie Lyons
Name of Person Mailing Paper — **Signature**

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Commissioner of Patents and Trademarks
Washington, DC 20231

Transmitted herewith for filing is the complete application for Patent Term Extension of United States Patent 4,902,683.

The filing fee is $1,060.00.

SPECIFIC DEPOSIT ACCOUNT AUTHORIZATION. Please charge my Deposit Account No. **21-0718** in the amount of the total filing fee above, or such greater or lesser amount as the Commissioner determines is required by law.

Respectfully submitted,

Date: 24 June 1996

Martha A. Gammill

Martha A. Gammill, Attorney
Registration No. 31,820
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